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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,825	09/10/2003	Jefferson C. Emery	GNE-0113A	6061
35489	7590	12/28/2010	EXAMINER	
Arnold & Porter LLP (24126) Attn: SV Docketing Dept. 1400 Page Mill Road Palo Alto, CA 94304			AUDET, MAURY A	
			ART UNIT	PAPER NUMBER
			1654	
			NOTIFICATION DATE	DELIVERY MODE
			12/28/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SV.Docketing@aporter.com

Office Action Summary	Application No. 10/659,825	Applicant(s) EMERY ET AL.	
	Examiner MAURY AUDET	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 November 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25 and 27-46 is/are pending in the application.
- 4a) Of the above claim(s) 27-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/9/10</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The Examiner extends Applicant an invitation to interview the application in January 2011 in order to work together on advancing the remaining issues towards allowable subject matter. Applicant may wish to consider cancelling without prejudice the withdrawn claims, which are not eligible for rejoinder under *In re Ochiai*, in response hereto.

As note previously, the present application has been transferred from former Examiner Shirali to the present Examiner.

Applicant's response (no amendments), arguments, are acknowledged.

Election/Restrictions

As noted previously, Applicant's election with traverse of Group I, claims 1-25, method of purifying a protein, in the reply filed on 2/1/07 is acknowledged. The traversal is on the ground(s) that, in summary, it would not be an undue burden since the former Examiner originally examined all the claims. This is not found persuasive for the reasons of record, and because restriction is proper at any time during prosecution, as warranted.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103-Traversed by Argument

The rejection of claims 1-25 under 35 U.S.C. 103(a) as being unpatentable over Genentech (Basey et al.; WO 99/57134) in view of Grandics et al. (US 5,571,720) and newly

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added reference, Winge (US 2001/0034053 A1, Priority Date 1/27/00), is traversed, Applicant's arguments have been fully considered and are found persuasive. Namely:

There is no motivation or suggestion to modify the cited references to reach the Applicants' invention.

The Examiner asserts that "varying the type of salt, amount (e.g. increasing OR decreasing concentration)" qualify as "routinely optimizable parameters." (Page 4 of the instant Final Office Action).

Applicants respectfully disagree. As described in the specification, the inventors found that the instantly claimed wash steps, performed in the order and using the parameters recited in the claims, were effective for polypeptide purification, particularly for resolving a desired polypeptide molecule from a contaminant differing only slightly in ionic charge.

As is recognized in ion exchange chromatography, the more similar the charge on the two molecules to be separated (polypeptide vs. contaminant), the more difficult it is to achieve a separation of the two molecules. The experimental examples in the patent application illustrate the use of the claimed methods to substantially reduce the amount of deamidated and other acidic variants in a purification of anti-HER2 antibody, which is a technically challenging separation owing to the very similar properties of the variants compared with the desired antibody polypeptide.

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The advantage that the instant method provides over the prior art is that, by **using a three slope gradient wash, a greater range of resin load densities are possible while maintaining product quality and not sacrificing yield**. The separation also becomes less sensitive to small variations in buffer composition. Washing steps are often employed to remove a contaminant from the column prior to elution, however, the resolution of species that a gradient wash would technically provide would not appear valuable to one skilled in the art since those species will never be collected. Moreover, multi-slope gradients are very complicated to run in a manufacturing environment and it would strike the unfamiliar process developer as pointless to incorporate such a complicated operation into a wash phase that will be discarded. As discussed above, development of the multi-slope gradient used in the instant method was the solution to the problem of achieving a wide resin load density range while maintaining yield and purity.

The achievement of this improvement in the load density range is a significant improvement over the prior art. A complicated series of interactions occur within the ion exchange column during the wash step and acidic variants are essentially just teased off the resin

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charge groups. At low resin load densities there are a large number of unoccupied resin binding sites that the acidic variants can loosely re-associate with, which means that from one run to the next, as the amount of protein loaded on the column varies, it can take a longer amount of time or require greater conductivity to get the acidic variants off the column. The three slope gradient of the instant method is a novel and non-obvious solution to this problem. Together the multi-slope gradient wash followed by the step elution provides a method to consistently remove acidic variants with a robust, reproducible process that can be effectively automated and scaled up. The prior art taken alone or in combination would not lead a skilled artisan to apply the multi-slope gradient to the wash step as instantly claimed.

Applicants reiterate that the cited art does not offer suggestions or even recognize a need for modification of their respective methods. In the absence of any recognized failure or shortcomings of these cited methods, the Examiner has provided no motivation for a protein research scientist to pursue any modifications, let alone provide a reasoning for selecting the specifically claimed method of the instant application over the multitude of possible salt gradient combinations possible.

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In summary, Applicants have shown that that the Examiner has not established a prima facie case of obviousness because: (1) the references cited by the Examiner do not teach or suggest protein purification via ion exchange chromatography employing different salt gradients during the washing phase, **wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough.** (2) there is no motivation or suggestion to modify the reference to reach the instant protein purification method because the references do not disclose protein purification via ion exchange chromatography **employing different salt gradients during the washing phase, wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough.** (3) there is no reasonable expectation of success that a combination of the references would succeed in producing a protein purification method utilizing ion exchange chromatography and **increasing salt gradients due to the lack of disclosure of washing steps employing increasing salt gradients during the washing phase, wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough,** and (4) the Examiner has based obviousness on improper hindsight. Accordingly, Applicants request that the rejection of Claims 1-25 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Basey et al. in view of Grandics et al. and further in view of Winge et al. be withdrawn.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments in the 103 rejection were persuasively put forth. Upon full consideration of these arguments, the metes and bounds of the invention are uncertain as to whether "**resin load densities**" – as discussed above - are an essential element/limitation that must be expressly incorporated into the claimed invention. Applicant is asked to clarify and amend the base claim if necessary to distinctly claim how managing the resin load densities as part of the invention is carried out.

Current base claim:

1. (Previously presented) A method for purifying a polypeptide from a composition comprising the polypeptide and contaminants, which method comprises the sequential steps of:
 - (a) loading the composition onto an ion exchange resin with an equilibration buffer having a first salt concentration;
 - (b) washing the ion exchange resin with a wash buffer until a predetermined protein concentration is measured in the flow through, wherein the salt concentration of the wash buffer increases from an initial, second salt concentration that is greater than the salt concentration of the equilibration buffer, to a final, third salt concentration;
 - (c) passing a fixed volume of wash buffer at the final, third salt concentration over the cation exchange resin; and
 - (d) eluting the polypeptide from the ion exchange resin with elution buffer that has a salt concentration that is greater than the final salt concentration of the wash buffer.

Applicant is asked to review the presently claimed invention to more distinctly claim the same, on this or any other points. The Examiner wishes to pick up with Applicant by Interview in January 2011 and go over any final proposed changes to more distinctly claim the invention as argued in the 103 rejection, towards advancing the application to allowance.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960.

The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 12/20/10

/Maury Audet/
Primary Examiner, Art Unit 1654